REMARKS

Claims 47-107 were previously submitted for examination. Claims 47-68 and 98-107 were withdrawn from consideration. Claims 1-46 were canceled by the Preliminary Amendment submitted on January 16, 2004 and claims 72-77, 85, 87-91 and 94 were canceled by the March 23, 2007 Amendment. Claims 69, 78 and 92 were amended by the September 17, 2007 Amendment. Claims 69, 70, 78, 86 and 92 have been amended, and new claims 108-127 have been added by the present Amendment. Therefore claims 69-71, 78-84, 86, 92, 93, 95-97 and 108-127 are under active consideration.

Support for the amended claims 69, 78 and 92 for reciting "a bioactive, three-dimensional epitope of a parathyroid hormone (PTH) in PTH_{1-8} or PTH_{1-9} sequence" can be found in the teachings in the original application of using a PTH_{1-8} peptide to purify an anti-PTH antibody (*See e.g.*, the present specification at page 11, lines 7-13), a whole PTH assay using an antibody that binds to an epitope within PTH_{1-9} sequence (*See e.g.*, Figure 2 of the present application), and an inherent binding property of an exemplary anti-PTH antibody used in the whole PTH assay as described in the present application, *e.g.*, at page 8, lines 24 and 25 of the present specification, and in Figure 11. This inherent binding property is described in Rebuttal Expert Report of Richard A. Lerner, M.D. (Lerner Report) (Exhibit B of the March 23, 2007 Amendment) at paragraph 5, pages 5-8 and Exhibits 2-7 of the Lerner Report.

Support for the amended claims 69, 78, 86 and 92 for reciting "said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment selected from a PTH_{1-8} fragment to a PTH_{1-34} fragment" can also be found in an inherent binding property of an exemplary anti-PTH antibody used in the whole PTH assay as described in the present application, *e.g.*, at page 8, lines 24 and 25 of the present specification, and in Figure 11. This inherent binding property is described in Rebuttal Expert Report of Richard A. Lerner, M.D. (Lerner Report) (Exhibit B of the March 23, 2007 Amendment) at paragraph 5, pages 5-8 and Exhibits 2-7 of the Lerner Report.

Support for the amended claims 70 and new claims 108-127 can be found in the teachings in the original application and in the inherent binding property of the exemplary anti-PTH antibody used in the whole PTH assay as discussed above for the amended claims 69, 78, 86 and 92.

Accordingly, the present amendments do not introduce any new matter. Entry of the amendments is respectfully requested.

With respect to all amendments and canceled claims, applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Withdrawn rejections

Applicants appreciate the Examiner's withdraw of the following rejections raised in the June 15, 2007 Office Action:

- The nonstatutory obviousness-type double patenting rejection over U.S. patent No. 6,689,566; and

- The written description rejection related to the "non-(1-86) PTH fragment" limitation.

Rejection under 35 U.S.C. § 112, first paragraph - New matter

The rejections of claims 69, 71, 78-84, 86, 92, 93, 95-97 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement are maintained. The Examiner alleged that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated:

> It is noted that the instant claim recites "an antibody binds to a bioactive, three-dimensional epitope of a parathyroid hormone (PTH), wherein said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment". No support from the specification can be found. Although applicant in the Remarks indicates the inherent characteristics of the antibody, particularly at page 8, line 24-25 and Figure 11, however no "three-dimensional" epitope PTH fragment was ever discussed in the whole specification (See Remarks page 13, fourth paragraph).

(December 13, 200 final Office Action at pages 2-3.)

Applicants respectfully traverse this rejection. It is a well established principle that by disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. MPEP § 2163.07(a) (emphasis added). The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *Id* (emphasis added).

In the present case, an exemplary antibody encompassed by the presently pending claims is disclosed in the present application and the parent applications. The Examiner also acknowledged that the experimental data provided by Dr. Lerner are "inherent" properties of the exemplary antibody, which indicate that the exemplary antibody binds to a three-dimensional epitope within a whole PTH with a higher affinity than its binding to the three-dimensional epitope within a PTH fragment. As such, the recitation of the "inherent" properties of the exemplary antibody in the presently pending claims does not introduce any new matter, and the present application and the parent applications provide adequate written description for the presently pending claims, albeit inherently by disclosing the exemplary antibody.

The Examiner also stated:

> Furthermore, applicant also submitted Dr. Lerner's binding analysis in support of the assertion with respect to the newly amended claims. Supra. (See Exhibit B). However, in view of the experimental

> conducted by Dr. Lerner, particularly #plate 2 in Exhibit 3, the binding activity of the whole PTH is even smaller than PTH fragment (1-34) and (37-82) (See rows B, C and F and column 11). This is contradictory to what Dr. Lerner described in the affidavit (See page 5 to page 6, particular page 6, second paragraph).

(December 13, 200 final Office Action at page 3.)

Applicants respectfully submit that the Examiner's reliance on the data shown on plate #2 of Exhibit 3 of Lerner Report is misplaced. As made clear at page 6, first paragraph of Lerner Report, the "PTH(1-9) antibody is referred to in some results as the 'N-terminal PTH' antibody." Also as made clear in Lerner Report, the antibody studied in connection with plate #2 is "GαH PTH (1-84) plasmas." This is not the exemplary "PTH(1-9) antibody" that is relied upon by the Applicants to show the inherent properties of the exemplary antibody, which indicate that the exemplary antibody binds to "a bioactive, three-dimensional epitope of a parathyroid hormone (PTH) in PTH_{1-8} or PTH_{1-9} sequence," and "said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment selected from a PTH_{1-8} fragment to a PTH_{1-34} fragment."

In addition to the data shown in Exhibit 3, Exhibit 2 of Lerner Report shows data indicating that the exemplary "PTH(1-9) antibody" has a higher binding affinity to the three-dimensional epitope within a whole PTH than its binding to the three-dimensional epitope within a PTH_{1-34} fragment. Similarly, Exhibit 5 of Lerner Report shows data indicating that the exemplary "PTH(1-9) antibody" has a higher binding affinity to the three-dimensional epitope within a whole PTH than its binding to the three-dimensional epitope within a PTH_{1-8} fragment or a PTH_{1-10} fragment. Therefore, the inherent properties of the exemplary antibody as shown in Lerner Report support the presently claimed invention.

The Examiner further stated:

> Examiner also found no definition of the three dimensional epitope is discussed in the specification. In the art, the term "three dimensional epitope" generally refers to a nonlinear discontinuous epitope. It is also called "conformation epitope" (See Moreau et al. Bioinformatics

> 2006 Vol. 22, page 1088-1095; Regenmortel et al. Methods in Enzymology 1996 Vol. 9, page 465-472). Regenmortal et al. describe that the three dimensional epitope is composed of several fragments scattered along the protein sequence and brought together in spatial proximity where the protein is folded (See Moreau et al., page 1088, right column; also See Regenmortel et al. page 468, Figure 1, model A). This is essentially similar to what applicant described in the Remarks (See page 13, second paragraph- *"because the conformational or three dimensional epitopes are formed from two or more stretches of polypeptide that are distant from one another in the primary structure, this means- that the conformational of the three dimensional epitopes are better formed when the entire protein is in its natural conformation (e.g. folding)*). Based upon such definition, the claim language of "said three-dimensional epitope within a PTH *fragment* cannot he true in the (1-9) PTH fragment since the 9 short amino acid residues peptide is a continuous *linear* peptide, not a three dimensional epitope (See affidavit Exhibit 3 data)(emphasis added).

(December 13, 200 final Office Action at page 3.)

Applicants respectfully submit that it is true that a three dimensional epitope is often formed by amino acid residues from different stretches of polypeptide that are distant from one another in the primary structure. However, the amino acid residues forming a three dimensional epitope need not necessarily be located on multiple polypeptides. Amino acid residues on the same polypeptide may also fold together to form a three dimensional epitope. For example, Fiskin et al., *J. Biol. Chem.*, 252(22):8261-8 (1977) (Exhibit A) analyzed images of parathormone obtained by dark field electron microscopy in order to determine the three-dimensional structure of the molecule. Based on their analysis, Fiskin et al. postulated a model for the PTH three dimensional structure or conformation. (*See* Figure 6 of Fiskin at page 8267, and page 8265, right col.) As shown in the model depicted in Figure 6, the PTH (1-8) or PTH (1-9) amino acid residues form an α-helix three dimensional structure or conformation. Therefore, contrary to the Examiner's assertion, the PTH (1-8) or PTH (1-9) amino acid residues within whole PTH can certainly form three dimensional epitopes.

The Examiner further stated:

> It is also noted that applicant claims a genus where an antibody "binds to a three-dimensional epitope of a PTH, wherein said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three dimensional epitope *within a PTH fragment*" (emphasis added). Assuming *arguendo*, both the (1-9) and (1-34) fragments do inherently contain a three dimensional epitope as declared by Dr. Lerner, nevertheless no experimental data on further C-terminal PTH fragments, e.g. 1-38, 1-40, 1-60, 1-70 and 1-80, are presented. The two fragments, i.e. 1-9 and 1-34 merely represent 40% of the whole PTH (full length 1-84 in humor, 1-86 in rat). Both species, at most, represent subgenus of the whole PTH. It has been held that a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads. see *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Taken together, the instant claims now recite a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

(December 13, 200 final Office Action at page 4.)

Applicants respectfully submit that the Examiner's concern is obviated by the present amendment indicating that "said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment selected from a PTH_{1-8} fragment to a PTH_{1-34} fragment."

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of this lack of written description/new matter rejection of the presently pending claims.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532212000624. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 12, 2008

Respectfully submitted,

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